

Optimal Operation Design of Continuous Enzymatic Reactor System

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連續酵素反應裝置의 最適反應操作設計

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ABSTRACT

The optimal operation problem of enzyme reactor of double inhibitions are dealt with Maximum Principle and Steepest Ascent Method. The operation policy of the initial concentration and amount of substrate, reaction time and the method of cross feed of substrate are determined in a system of reactor of constant volume and with cross feed of substrate.

The policy for the soluble enzyme and the immobilized enzyme are greatly different from each other, and the performance index, the profit per unit time, of the latter are nearly twice greater than that of the former.

INTRODUCTION

Recently Ryu and Lee¹⁾ have developed a kinetic model of an enzymatic reaction with competitive and non-competitive double inhibitions. The simulation studies have been carried out on the single-stage continuous stirred tank reactor system and CSTR-Separator Combination enzyme reactor system using the experimentally determined kinetic constants.

However, from the practical point of view, the device for continuous enzyme separation to recycle or retain the used enzyme in the reactor vessel proposed by Ryu et al is limited to use the ultra-filter membrane, which would be a technical

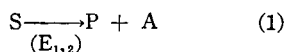
bottleneck in scaling up the CSTR to the industrial plant scale.

The author is interested in the optimization problem of the systems involving the same complex reaction mechanism and the more practical modes of reactor system operation.

In the present research project, an alternative type of reactor system and its control mode of operation which enable the maximization of the economical productivity were studied. At first, a semi-batch reactor system was conceived in the Continuous Stirred Tank Reactor with Cross Feeds, because a semi-batch reactor is equivalent to an infinite multi-stage CSTR when the reactor efficiency is taken into account.

KINETIC MODEL AND RATE EQUATIONS

Consider a reaction of substrate S promoted by enzyme $E_{1,2}$ which has the two of different functional catalytic active sites, to produce product P and by-product A, which act as the non-competitive and competitive inhibitors respectively.



In equations (2) through (8), the elementary

reaction steps are summarized. The individual reaction rate constants to be evaluated were organized as shown in equations (9) through (11). To fit the standard experimental methods of determining Michaelis-Menten's constant K_m , non-competitive inhibition constant K_{iP} , and competitive inhibition constant K_{iA} , the concentration of substrate is assumed to be very large compared to the total enzyme concentration E_0 which is defined as the sum of the concentrations of free enzyme $E_{1,2}$ and that of the five kinds of enzyme complexes $(S \cdot E_2)$, $(P \cdot E \cdot S)$ etc. (c.f. Fig. 1)

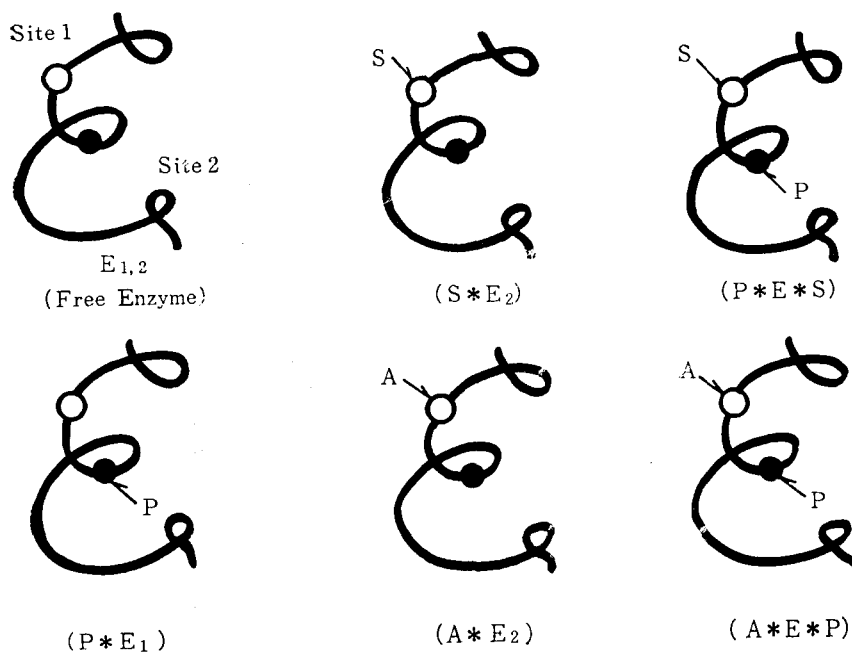
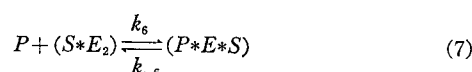
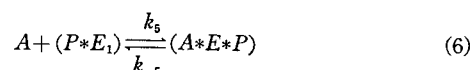
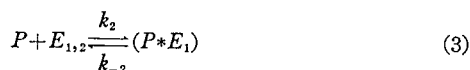
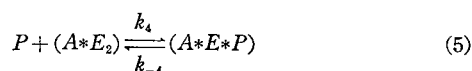
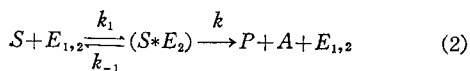


Fig. 1 Enzyme Complexes and their symbols cited.



$$S + (P \cdot E_1) \xrightleftharpoons[k_{-7}]{k_7} (P \cdot E \cdot S) \quad (8)$$

and

$$K_m \equiv \frac{k_{-1}}{k_1} \simeq \frac{k_{-7}}{k_7} \quad (9)$$

$$K_{iP} \equiv \frac{k_{-2}}{k_2} \simeq \frac{k_{-4}}{k_4} \simeq \frac{k_{-6}}{k_6} \quad (10)$$

$$K_{iA} \equiv \frac{k_{-3}}{k_3} \simeq \frac{k_{-5}}{k_5} \quad (11)$$

The overall rate expression was derived as is shown in equation (12) under the condition of steady state.

$$R = \frac{kE_o}{1 + \frac{K_m}{S} \left(1 + \frac{A}{K_{iA}}\right) + \frac{P}{K_{iP}} \left(1 + \frac{K_m}{S}\right)} \sim \frac{AP}{S} \left(\frac{K_m}{K_{iA}K_{iP}}\right) \quad (12)$$

And when enzyme loading $k_e (=kE_o)$, equilibrium constants K_m , K_{iA} and K_{iP} are experimentally determined on an individual basis, the overall rate equation is formulated as a function of the values of enzyme loading k_e , initial substrate concentration S_o and the conversion factor of substrate S defined in equation (13).

$$X(t) = \frac{S_o - S(t)}{S_o} \quad (13)$$

Approximately, the concentrations of products P and A are taken to be equal, neglecting the concentrations of enzyme complexes compared with those of substrate and products

$$A \simeq P \simeq S_o X \quad (14)$$

Substituting equations (13) and (14) for eq. (11), reaction rate R is expressed as a function of initial substrate concentration S_o and its conversion factor X , which is the function of reaction time and the factors such as operational and/or

control variables, flow pattern of enzyme reactor, rate of recycles, rate of make-up, etc.

$$R = \frac{kE_o S_o \cdot (1-X) K_{iA} K_{iP}}{PA(1) + PA(2) + PA(3) + PA(4) + PA(5) + PA(6)} \quad (15)$$

where

$$PA(1) = K_{iA} K_{iP} S_o (1-X)$$

$$PA(2) = K_m K_{iA} K_{iP}$$

$$PA(3) = K_m K_{iP} S_o X$$

$$PA(4) = K_{iA} S_o^2 (1-X) X$$

$$PA(5) = K_m K_{iA} S_o$$

$$PA(6) = K_m S_o^2 X^2$$

To express conversion factor X as a function of the time factor (reaction time/residence time) under the constant operation variables, equation (16) is solved using Newton-Raphson's method, for instance.

$$f(X) = AX^3 + BX^2 + CX + D = 0 \quad (16)$$

where

$$A = \{(K_m - K_{iA}) S_o^2\}$$

$$B = \{K_{iA} S_o^2 + (K_m K_{iA} K_m K_{iP} - K_{iA} K_{iP}) S_o\}$$

$$C = \{K_{iA} K_{iP} S_o + (K_m K_{iA} K_{iP} + K_{iA} K_{iP} R_{max} \cdot \tau)\}$$

$$D = \{-R_{max} K_{iA} K_{iP} \cdot \tau\}$$

OPTIMIZATION PROBLEM

1. STATEMENT OF THE PROBLEM

Initially, substrate solution of concentration S_o and an amount of enzyme to get certain value of enzyme loading is fed into the reactor tank. Then the volume of reactor varies with the additional feeding of substrate solution $F(t)$ of concentration $D(D) > S_o$ which is programmed by the optimization policy during the reaction time from $t=0$ to $t=t_F$. The finishing time t_F is also

determined as a result of optimization study to maximize the objective function usually taken as an index of economical benefit of the production process per unit time.

The system to be optimized is illustrated in Fig. 2. Hence we are to design the reactor operation according to the optimal policy whose

control variables are the initial amount of the substrate S_0 , reaction time t_F and the policy of the cross feed of concentrated substrate during the time of reaction $F(t)$. The performance index I, defined as the gross profit per unit time per unit volume of reactor during the operation cycle, is expressed by the following equation (18).

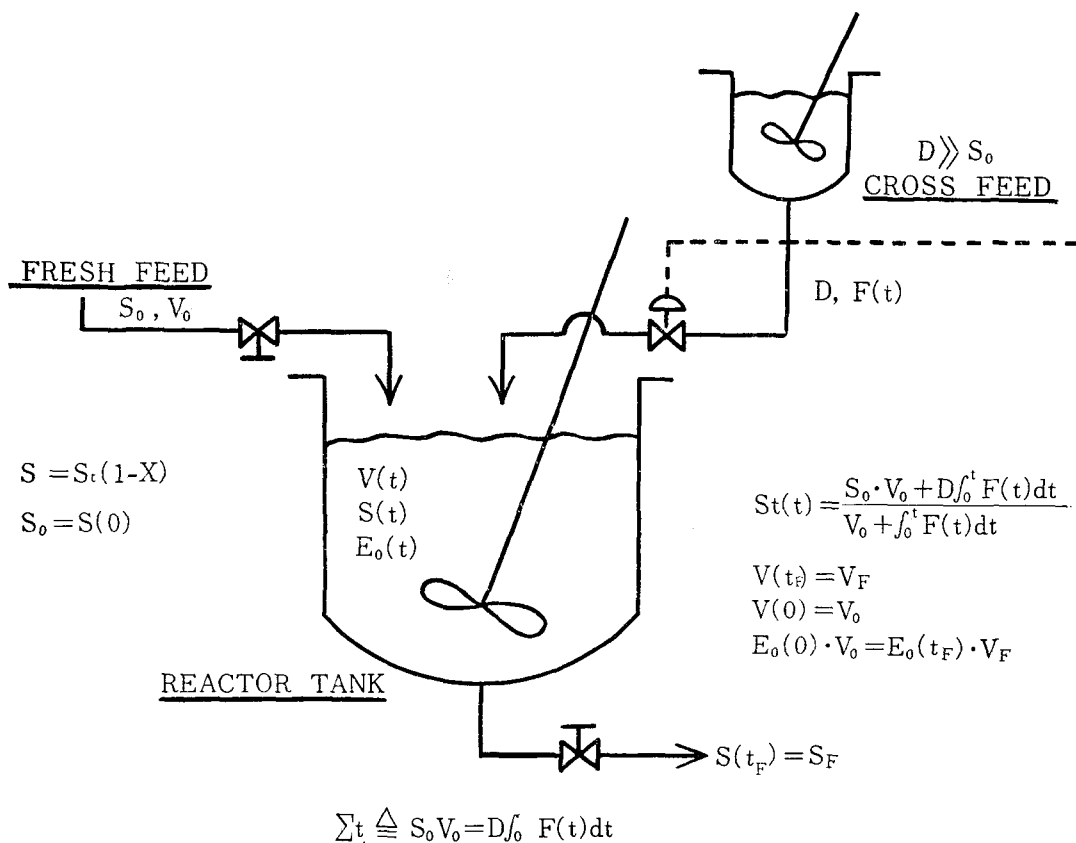


Fig. 2. Schematic Diagram of the Semi-Batch Reactor System Studied.

$$\begin{aligned}
 I &= \frac{C_P \cdot P_F V_F - C_S [(V_F - V_0) D + V_0 \cdot S_0]}{t_F + t_M} \\
 &= \frac{(C_P - C_S) \cdot (V_0 S_0 + (V_F - V_0) D) - C_P \cdot V_F S_F}{t_F + t_M}
 \end{aligned}
 \tag{18}$$

where, C_P = unit price of main product
 C_S = unit price of substrate
 V_F = volume of reactor at $t = t_F$
 V_0 = volume of reactor at $t = 0$
 P_F = concentration of main product at $t = t_F$
 S_0 = concentration of substrate at $t = 0$
 S_F = Concentration of substrate at $t = t_F$

D = concentration of substrate of the cross-feed
 t_F = reaction time
 t_M = time of maintenance per cyclic operation.

Because the numerical value of the fourth term in the denominator of equation (12) is largely less than 1.0, the rate expression (12) can be rearranged as equation (19), in terms of the total amount of substrate fed into the reactor tank $\sum t$, final volume V_F , and substrate concentrator

S and the reactor volume V at the time t ;

$$R(S, V) = \frac{kE_0(t_F)S(V/V_F)}{S + K_m \left[1 + \frac{\{\sum_i - V_F D + (D-S)V\}}{K_{iA} \cdot V} \right]} \sim \frac{(S + K_m)}{K_{iP}} \cdot \frac{\{\sum_i - V_F D + (D-S)V\}}{V} \quad (19)$$

where $E_0(t_F)$ = Enzyme concentration at $V = V_F$

$$\begin{aligned} \sum_i &= S_0 V_0 + D \int_0^{t_F} F(t) dt \\ &= S_0 V_0 + D(V_F - V_0) \end{aligned}$$

MAXIMUM PRINCIPLE APPROACH

By assuming that substrate loading \sum_i , initial substrate concentration S_0 and initial reactor volume V_0 , the optimal cross feed policy of substrate $F(t)$ would be determined by the maximum principle. Since the rate equation is shown in eq. (19), when we neglect the complex intermediates compositions of the enzyme, the concentration of product P and by-product A , and enzyme E in the reactor can be expressed as the functions of substrate concentration S and reactor volume V . And also we can define $V(t)$ and $S(t)$ as functions of reaction time only. The state equations for these two state variables are as follows;

$$\frac{dV}{dt} = T_1(t) = F(t) \quad (20)$$

$$\frac{dS}{dt} = T_2(t) = (D-S) \frac{F(t)}{V(t)} - R(S, V) \quad (21)$$

Let us take adjoint variables of the state variables V and S , as ω and Z respectively, then the adjoint system equations can be expressed as shown in (22) and (23).

$$\begin{aligned} \frac{d\omega}{dt} &= -\frac{\partial T_1}{\partial V} \omega(t) - \frac{\partial T_2}{\partial V} z(t) \\ &= \left\{ (D-S) \frac{F}{V^2} + \frac{\partial R}{\partial V} \right\} \cdot z(t) \quad (22) \end{aligned}$$

$$\begin{aligned} \frac{dz}{dt} &= -\frac{\partial T_1}{\partial S} \omega(t) - \frac{\partial T_2}{\partial S} z(t) \\ &= \left(\frac{\partial R}{\partial S} + \frac{F}{V} \right) z(t) \quad (23) \end{aligned}$$

To maximize the performance index I ($V_F S_F$), the boundary conditions for ω_F and Z_F are; ^{3,4)}

$$\omega_F = \omega(t_F) = \frac{\partial F}{\partial V_F} \Big|_{t=t_F} = \frac{(C_P - C_S)D - C_P S_F}{(t_F + t_M)} \quad (24)$$

$$z_F = z(t_F) = \frac{\partial I}{\partial S} \Big|_{t=t_F} = \frac{-C_P V_F}{(t_F + t_M)} \quad (25)$$

where
$$\frac{\partial \omega}{\partial t} = -\frac{\partial \mathcal{H}}{\partial V}$$

$$\frac{dz}{dt} = -\frac{\partial \mathcal{H}}{\partial S}$$

From the definition of Hamiltonian function, ^{2,4)} the Hamiltonian of this system, \mathcal{H} is written as follows;

$$\begin{aligned} \mathcal{H} &= \omega T_1 + z T_2 = \omega F + z \left\{ (D-S) \frac{F}{V} - R(S, V) \right\} \\ &= \left(\omega + \frac{D-S}{V} z \right) \cdot F - R \cdot z \quad (26) \end{aligned}$$

As is shown in equation (26) \mathcal{H} has its maximum value when F is controlled so that performance index I becomes maximum. Since \mathcal{H} is the first order linear equation in terms of F , the optimal policy becomes the mode of the bang-bang control and is described as follows.

$$\left. \begin{aligned} F &= F_{max} \text{ for } \omega + \frac{D-S}{V} z \geq 0 \\ F &= 0 \text{ for } \omega + \frac{D-S}{V} z < 0 \end{aligned} \right\} \quad (27)$$

The terms $\partial R/\partial S$, $\partial R/\partial V$ involved in equations (22) and (23) are found by partially differentiating eq. (19) with V and S respectively, the results are shown in equations (28) and (29).

$$\partial R/\partial V = -(A_0/A_4) \cdot [A_3 + A_2(D-S)] \quad (28)$$

$$\partial R/\partial S = (A_0/S) \cdot \left[1 - \frac{1}{A_4} (1-A_2) \cdot V + \left(\frac{A_1}{K_{iP}} \right) \right] \quad (29)$$

where

$$\begin{aligned}
A_0 &= KE_0 F - S/A_4 \\
A_1 &= A_5 - V_F D + (D - S) V \\
A_2 &= K_m K_{iA} + (S + K_m)/K_{iP} \\
A_3 &= S + K_m \\
A_4 &= A_3 V + A_1 A_2 \\
A_5 &= V_F S_F / X
\end{aligned}$$

ALGORITHM

In this problem, the initial values of the state variables V_0 and S_0 are taken arbitrarily, but the final state variable V_F is fixed instead. Therefore the corresponding adjoint variables of S_0 and V_0 have the vanishing boundary conditions whereas that of V_F is unspecified. And the numerical calculations for the solution become rather complicated. So we derive the optimal policy by assuming that the initial variables are all specified. The maximum principle is applied to the set

of assumed final state variables and fixed state variables, which is then integrated to get the initial state variables V_0 and S_0 from $t=t_F$ to $t=0$.

So the initial state variables are determined by the inverse integration carried out starting from the final values of the state variables. As V_F has a fixed value, we predetermine the total amount of substrate Σ_t and the final conversion X_F according to the following formula and calculate optimal policy by using those values,

$$X_F = 1 - \frac{V_F S_F}{\Sigma_t}$$

The flow chart of the subprograms of the above calculations is illustrated in Fig. 4 and the brief descriptions about the function of each subprogram are as following.

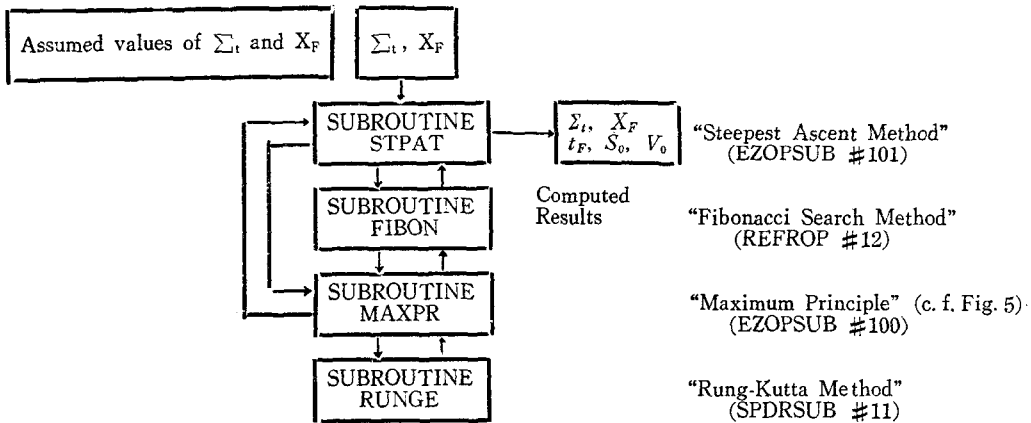


Fig. 4 The Organization of Executed "Package Program" (EZOPSUB #100) for IBM-1130. (Referenced subprograms are available for distribution on request)

1) Subroutine STPAT

From the given Σ_t and X_F , by using the Method of Steepest Ascent, we are to determine the direction in the $\Sigma_t - X_F$ space along which the increase of the value of I is maximum, and to find the maximum point of I in that space finally.

2) Subroutine FIBON

By Fibonacci Search Method we find the point

(Σ_t, X_F) at which I is the local maximum along the direction axis of $\Sigma_t - X_F$ space determined in the above subroutine STPAT just before.

3) Subroutine MAXPR

- (1) Calculate S_F by using given values of Σ_t and X_F .
- (2) Calculate ω_F and z_F by the equations (24) and (25) in terms of S_F and V_F in the case of $t_F=0$.
- (3) Substitute the result for (27) and determine

F.

- (4) Integrate (20) to (23) in the time range of $(-\Delta T)$ by Runge Kutta Method.⁶⁾
- (5) To check whether the integration carried out to the initial state could regenerate the initial (assumed) values in the allowable error range, calculate the value of an error detecting term E , where

$$E = \frac{\sum_i (1-V)D_i - S}{V}$$

- (6) If $E > 0$, continue the calculations (3), (4) and (5) because of the lack of physical

meaning.

If $E < 0$, compute performance index I .

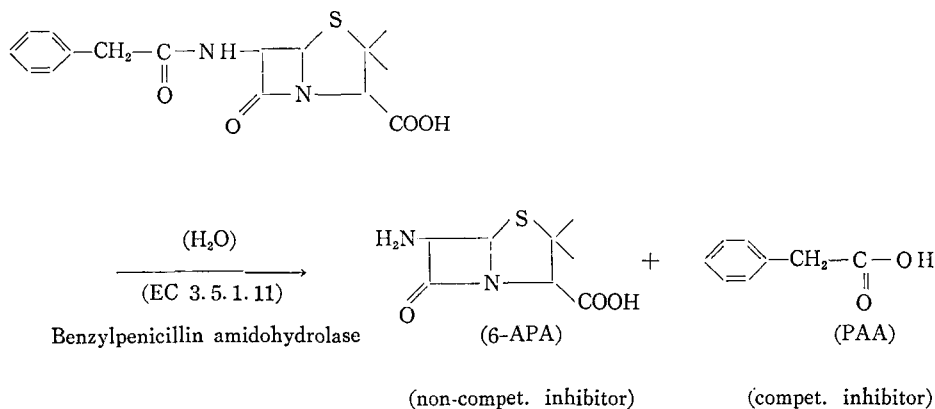
4) Subroutine RUNGE

Simultaneous differential equation is numerically integrated by Runge-Kutta Method.

NUMERICAL EXAMPLE

Kinetic constants and scheme of the reaction used in this study are summarized in Table 1 below.

REACTION SCHEME



Kinetic Data	Soluble Enzyme	Immobilized Enzyme
K_m	0.0045 [kgmol/m ³]	0.0060 [kgmol/m ³]
K_{ip}	0.0260 "	0.2500 "
K_{iA}	0.4500 "	0.6200 "

OPERATION CONDITION		
$C_p/C_s=6.$	$D=2$ [kgmole/m ³]	$F_{\max}=0.02$ m ³ /hr
$V_F=1$ m ³	$T_M=0.5$ hr	$k \cdot E_{oF}=0.35$ kg-mole/m ³ ·hr

Table 1. Reaction Scheme and Kinetic Constants

In Fig. 6 and Fig. 7, the change of reaction rate with respect to initial substrate concentration S_0 and conversion X for both systems of immobilized and soluble enzyme with no cross feed of substrate. As shown in those figures, the ideal reaction path deviates from the line of constant initial

concentration of substrate such that a certain feed policy of substrate could bring the maximization of the profit.

In Fig. 8 the maximum point $(\sum_i X_F)_{\text{opt}}$ is approached by the Steepest Ascent Method. In Fig. 9 the maximum performance index I is

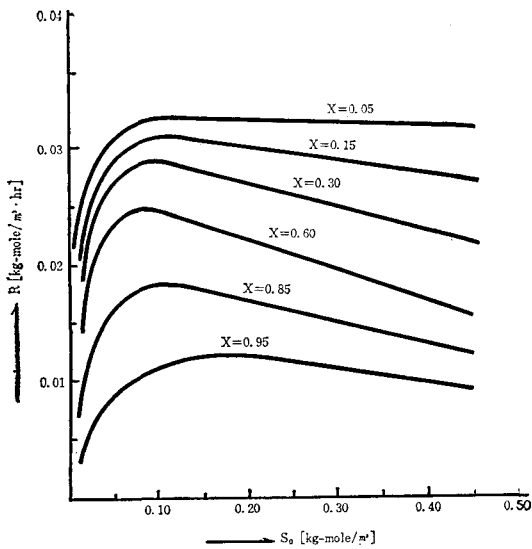


Fig. 6. Reaction Rate vs. Initial Substrate Concentration (Immobilized Enzyme)

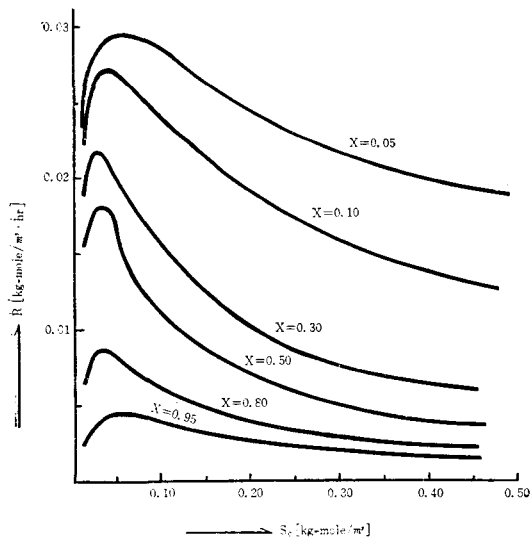


Fig. 7. Reaction Rate vs. Initial Substrate Concentration (Soluble Enzyme)

determined by Fibonacci search method along the direction determined by the use of steepest ascent method (for the easy calculation I/C_p is used here instead of I).

As shown in Fig. 8 those contours of I in the $\Sigma_t - X_F$ space are very compact when $X_F \geq 0.8$. This is also demonstrated with the curve in the Fig. 9 whose inclination is steep in that region.

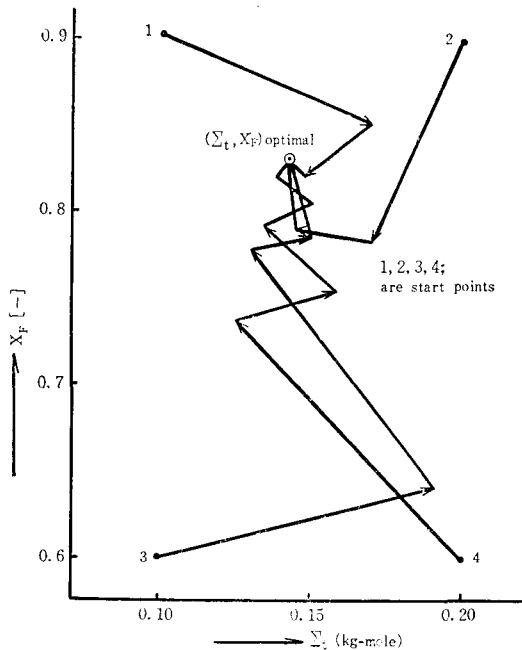


Fig. 8. Interaction trajectories of Steepest Ascent Method (the Immobilized Enzyme.)

The optimal policy calculations followed by these procedures are shown in Table 2 below.

Table 2. Optimal Operation Policy

	Σ_t : [k-gmole]	X_F	$F(t)$: [m³/hr]	t_F [hr]	I [1/hr]
Soluble	0.04928	0.72636	0.0*	2.0384	0.06519
Immobilized	0.14126	0.83142	0.0*	4.5766	0.11096

**No feed throughout $t=0$ to t_F

As is shown in the Table 2 there is a great difference between the optimal policy of immobilized enzyme and that of soluble to such an extent that performance index I is about two times as large for the immobilized as for the soluble. But the result indicates that there is no side stream, which we have expected to be. However in the calculation process there are some side streams as in Figs. 11 and 12 for the case of non-optimal policy but as the local optimum point (Σ_t, X_F) , exceptionally. In Figs. 13 and 14 the substrate concentrations and corresponding changes of reaction rate with respect to reaction time in the case of the two converged optimal policies were shown. The bird-eye-view of the Performance index I is shown in Fig. 10. over the plane of (Σ_t, X_F) .

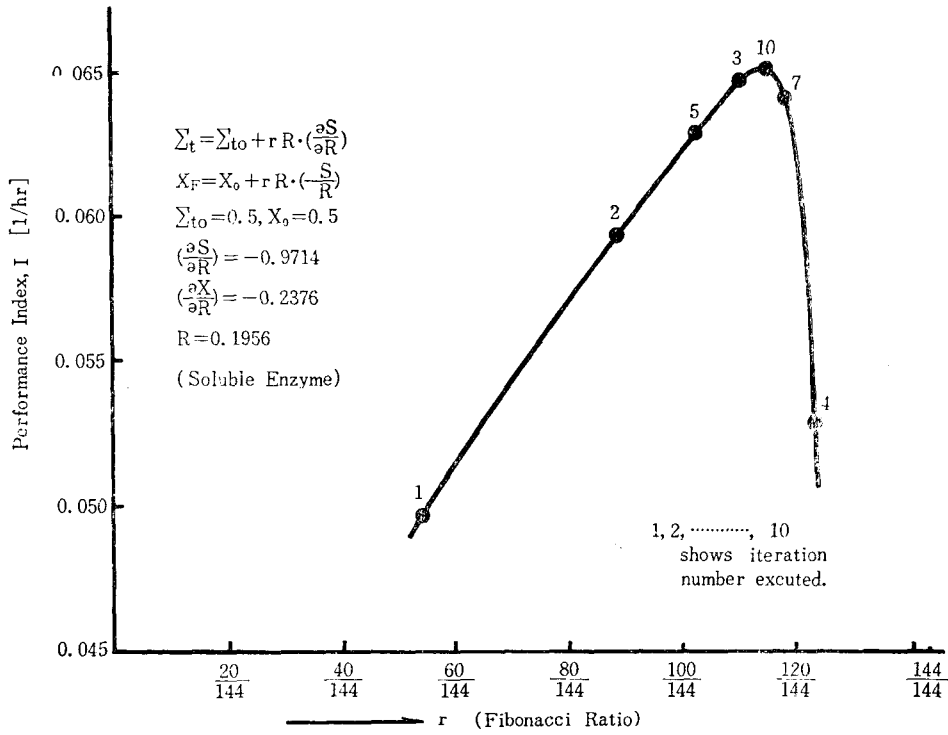


Fig. 9. Fibonacci Search Method

(The numbers noted in the fracket the order show of searching calculation.)

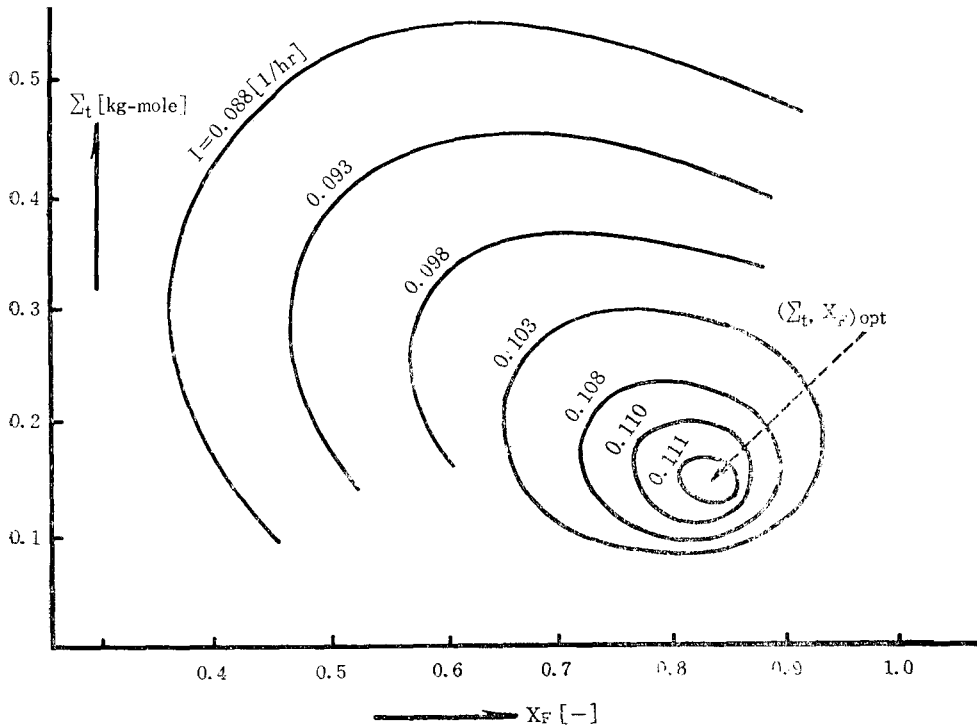


Fig. 10. The contours of I in $\Sigma_t - X_F$ Space (Immobilized Enzyme)

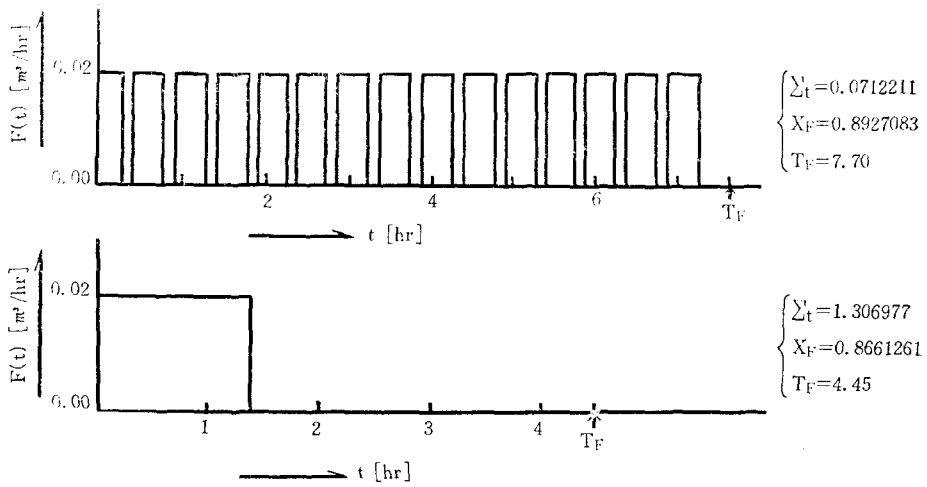


Fig. 11. Typical Examples of Optimal policy of Side Feed, $F(t)$. (Immobilized Enzyme)

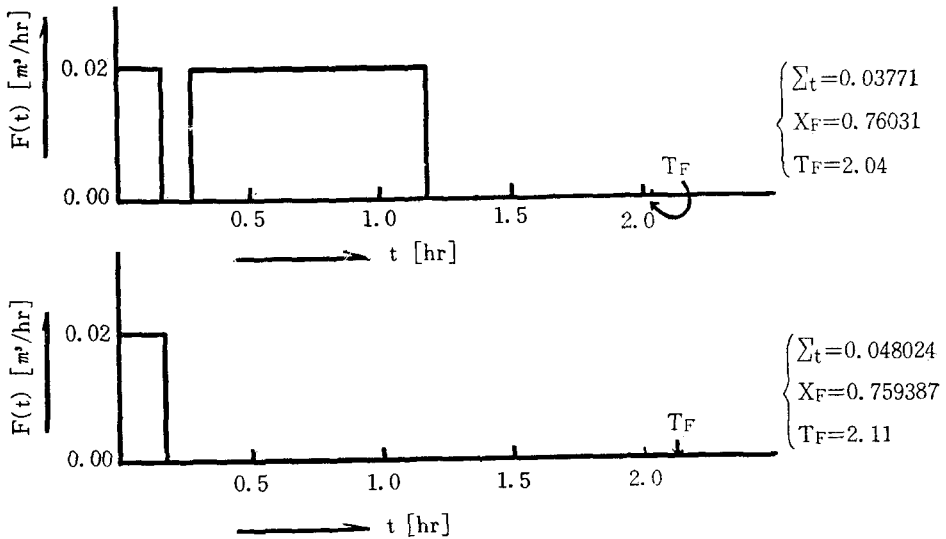


Fig. 12. Typical Examples of Optimal Policy of Side Feed, $F(t)$. (Soluble Enzyme)

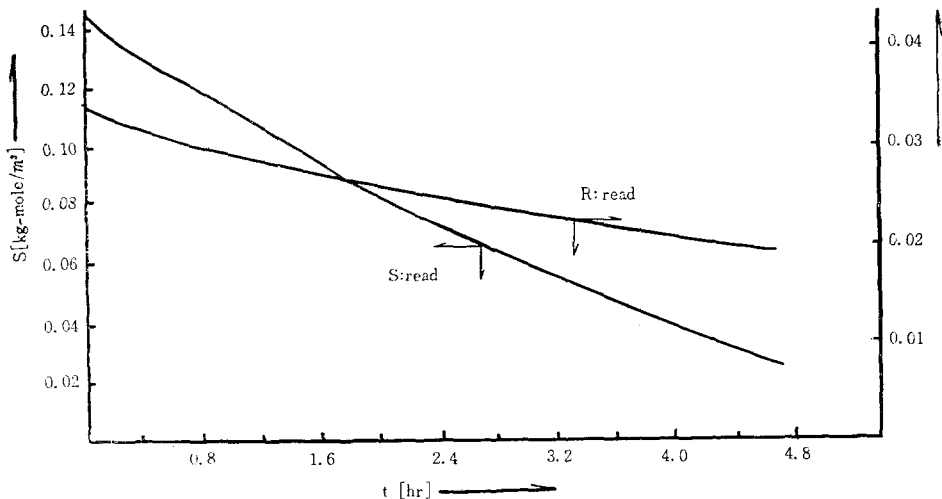


Fig. 13. Reaction Rate and Substrate Concentration vs. Reaction time. (Immobilized Enzyme)
 $\Sigma t = 0.14126$, $X_F = 0.83142$

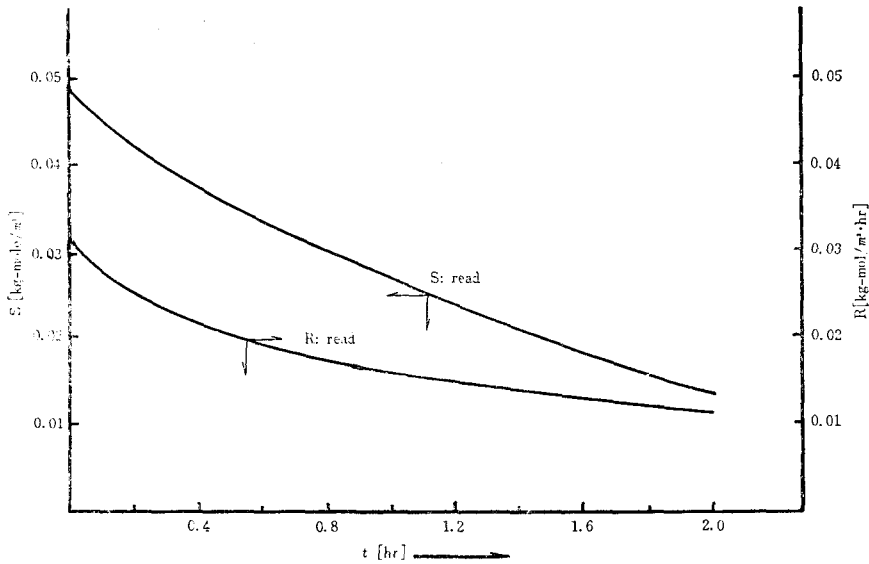


Fig. 14. Reaction Rate and Substrate Concentration vs. Reaction Time.

(The of Soluble Enzyme) $\Sigma_i=0.04928$, $X_F=0.76236$

CONCLUSION AND DISCUSSION

The optimal condition for a semi-batch reactor system was investigated by using the maximum Principle and the Steepest Ascent Method. The optimal policies determined were quite different from each other in their performance index I when soluble and immobilized enzyme were used. And at the optimal point no side feed was required.

The further researches are left on the study of ultra-filter element as a filtration device, enzyme separation and purification of 6-APA and multistaged reactor design.

要 約

가장 복잡한 반응機構를 갖은 효소反應의 例로서, 生成物에 의한 非拮抗 및 拮抗 2重阻害를 입는 효소反應의 경우에 對하여 連續酵素反應裝置의 反應 操作을 Pontryagin의 連續型最大原理에 依하여 研究하여 얻은 最適設計法을 報告하였다. 設計例로서 柳斗榮 等의 報文¹⁾에 發表된 反應速度에 關한 data를 使用하여 合成 Penicilline의 中間體인 6-APA 合成反應工程의 경우를 다루었다.

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Nomenclature

A : Concentration of by-product [kg-mole/hr]	S : concentration of substrate [kg-mole/m ³]
C_p : Unit Cost of product [\$/kg-mole]	S_0 : concentration of substrate at $t=0$ [kg-mole/m ³]
C_s : Unit Cost of Substrate [\$/kg-mole]	S_F : Concentration of substrate at $t=t_F$ [kg-mole/m ³]
D : Unit Substrate concentration of the cross feed [kg-mole/m ³]	Σ : Total substrate loading [kg-mole]
E_{12}, E_1, E_2 : Intermediate enzyme complexes [c. f. Fig. 1]	t : Time [hr]
E_0 : Total enzyme concentration [kg-mole/m ³]	t_F : reaction time [hr]
$F(t)$: Side stream flow rate [m ³ /hr]	t_M : reactor maintenance time per cycle of reaction [hr]
F_{max} : Maximum flow rate of side stream [m ³ /hr]	T_1 : differential transformation of V [m ³ /hr]
\mathcal{H} : Hamiltonian c. f. eq (26) [1/hr ²]	T_2 : differential transformation of S [kg-mole/m ³ ·hr]
I : performance Index [\$/hr], [1/hr]	ΔT : time interval for the numerical integration [t]
K : reaction rate constant [m ³ /kg-mole·hr], [1/hr]	V_0 : Volum of Reaction system at $t=0$ [m ³]
K_m : Michaelis-Menton constant [kg-mole/m ³]	V_F : Volume of Reaction system at $t=t_F$ [m ³]
K_{ip} : Inhibition constant of P [kg-mole/m ³]	ω : adjoint variable corresponding to V [1/m ³ ·hr]
K_{iA} : Inhibition constant of A [kg-mole/m ³]	ω_F : ω at $t=t_F$ [1/m ³ ·hr]
D : Concentration of substrate of cross feed [kg-mole/m ³]	X : conversion factor [—]
P_F : Concentration of product at $t=t_F$ [kg-mole/m ³]	X_F : X at $t=t_F$ [—]
R : reaction rate [kg-mole/m ³ , hr]	Z : adjoint variable corresponding to S [m ³ /hr·kg-mole]
	Z_F : Z at $t=t_F$ [m ³ /hr·kg-mole]

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C      OPTIMIZATION OF ENZYME REACTOR SYSTEM "PACKAGE PROGRAM"
C      : (EZOPSUB #100)
C      PROF. SHIK NAMKOONG, CHEM.ENG.DEPT., S.N,U.
C      JAN.      , 1974

```

```

COMMON CK, CKM, CKIP, CKIA, CPCS, D, FMAX, TW, DT, TMAX, CS, CG

```

```

READ(2,9)      MMM
READ(2,202)    CK,CKM,CKIP,CKIA
READ(2,202)    CPCS,D,FMAX,TW
READ(2,202)    XO,SO,DX,DS,XL,XH,SL,SH,TMAX
READ(2,202)    RX,RS,DT,G
READ(2,203)    IT,N,ERR
READ(2,202)    CS,CG

```

C

```

WRITE(3,301)
WRITE(3,310)   CK,CKM,CKIP,CKIA
WRITE(3,302)
WRITE(3,310)   CPCS, D,FMAX,TW
WRITE(3,304)
WRITE(3,340)   RX,RS,DT,G,IT,N,ERR
WRITE(3,303)
WRITE(3,320)   XO,SO,DX,DS,XL,XH,SL,SH,TMAX
WRITE(3,305)   CS,CG

```

C

```

GO TO (1,2),MMM
1  CALL MAXPR (XO,SO,P,1,2)
GO TO 3
2  CALL STPAT (XO,SO,DX,DS,RS,RX,SL,SH,SL,SH,G,ERR,IT,N,KP)
3  CONTINUE

```

C

```

9  FORMAT (15)
202 FORMAT (5F16.8)
203 FORMAT (211C,F10.0)
310 FORMAT (20X,8F, 12.5//)
320 FORMAT (8X,9F 12.5/)
340 FORMAT (20X,4F 12.5,218,F12.5)
301 FORMAT (5X,20H REACTION RATE CONST.,6X,1HK,10X,2HKM,9X,3HKIP,9X,
1 3HKIA)
302 FORMAT (5X,20H OPERATION CONDITION, 2X,5HCP/CS,11X,1HD,8X,4HFMAX,
1 10X,2HTW)
303 FORMAT (18X, 2HXO,10X,2HDX,10X,2HDS,10X,2HXL,10X,2HXX,
1 10X,2HSL,10X,2HSX,8X,4HTMAX)
304 FORMAT (5X,20H CALCULATION CONST. , 5X,2HRX,10X,2HRS,10X,2HDT,11X,
1 1HC,8X,2HIT,7X,1HN,6X,3HERR)
305 FORMAT (18X,2HCS,10X,2HCG,/,8X,2F 12.5)

```

C

```

CALL EXIT
END

```

```

C      SUBROUTINE MAXPR (X,S,P,N,NP) : (EZOPSUB #102)
C      OPTIMIZATION OF ENZYME REACTOR BY MAXIMUM PRINCIPLE
      DIMENSION Y(4), DY(4), G(28), TSW(50)
      COMMON C,CM,CIP,CIA, COST,D,FM,TW,DDT,TMAX,CS,CG
      T=0
      Y(1)=1.
      Y(2)=S*(1 -X)
      Y(3)=(1 -1./COST)*D-Y(2)
      Y(4)=-1
      F=0.
      FL=0
      NSW=0
      IF(NP-2) 21,15,21
15     WRITE (3,1)
21     L=3
      M=0
23     CALL RUNGE (T,DT,4,Y,DY,G,L,M,J)
      IF (M-1) 24,28,24
24     GO TO (25,26),L
28     IF(Y(2)) 131,131,98
131    T=T-DT
      Y(1)=VL
      Y(2)=SL
      Y(3)=WL
      Y(4)=ZL
      GO TO 31
98     SNF = Y(3)+(D-Y(2))*Y(4)/Y(1)
      IF (SNF) 31,32,32
31     F=0.
      GO TO 33
32     F=FM
33     IF(F-FL) 61,21,61
61     NSW=NSW+1
      TSW(NSW)=T
      FL=F
      GO TO 21
25     A1=S-D+(D-Y(2))*Y(1)
      A3=Y(2)+CM
      A2=CM/CIA+A3/CIP
      A4=A3*Y(1)+A1*A2
      R =C*Y(2)/A4
200    RV=-R*(A3+A2*(D-Y(2)))/A4
      RS=R*(1.-A2)*Y(1)+A1/CIP)*Y(2)/A4)/Y(2)
125    DY(1)=F
      DY(2)=F*(D-Y(2))/Y(1)-R
      DY(3)=(DY(2)+R)/Y(1)+RV)*Y(4)
      DY(4)=(F/Y(1)+RS)*Y(4)
      GO TO 23
26     E=(S-(1.-Y(1))*D)/Y(1)-Y(2)
      IF (NP-2) 29,27,29

```

```

27 WRITE (3,2) T,F,Y,R,SNF,E
29 IF (T+TMAX) 40,41,41
40 GO TO (43, 90), NP
43 NP=2
GO TO 15
90 STOP
41 IF (E) 47,47,46
46 IF(F) 82,82,81
81 IF(DY(2)) 87,87,83
83 DTS=-Y(2)*CS/DY(2)
GO TO 89
82 DG=(RV+(D-Y(2))*RS/Y(1)+R/Y(1))*Y(4)
IF(DG) 84,87,87
84 DTS=-SNF*CG/DG
89 IF(DTS) 85,85,87
85 IF (DTS+DDT) 87,86,86
86 NT=1.-10.*DTS/DDT
DT=-0.1*NT*DDT
GO TO 23
87 DT=-DDT
146 EL=E
SL =Y(2)
VL =Y(1)
WL=Y(3)
ZL=Y(4)
GO TO 23
47 IF (NP) 48,48,49
49 WRITE (3,3)
48 ER=E/(E-EL)
T=T-DT*ER
Y(1)=Y(1)-(Y(1)-VL)*ER
Y(2)=Y(2)-(Y(2)-SL)*ER
B=(S-(1.-Y(1))*D)/S
DO 60 I=1, NSW
60 TSW(I)=TSW(I)-T
P=(COST*X-1.)*S/(TW-T)
WRITE(3,4)N,S,X,P,B,Y(2),Y(1),T
IF(NSW) 72,72,71
71 WRITE (3,5) (TSW(I),I=1,NSW)
72 RETURN
1 FORMAT (1H1///6X,1HT,11X,1HF,11X,1HV,11X,1HS,11X,1HW,11X,1HZ,11X,
11HR,11X,1HG,11X,1HE//)
2 FORMAT (9F12.6)
3 FORMAT (/// 3X,3HNO.,11X,1HS,11X,1HX,11X,1HP,11X,1HB,10X,2H50,10X,
1 2HVO,10X,2HTF /15X,3HTSW / )
4 FORMAT (15,6X, 8F 12.7)
5 FORMAT (5X,10F11.6)
END

```